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REMARKS/ARGUMENTS

Claims 1-10, 12, 14, 15 and 18-23 are pending in this application. In a non-final Office Action mailed March 12, 2007, the Patent Office objected to the specification and to claim 22, and rejected all of the pending claims.

I. Objections to the Specification and Claims

The specification has been objected to as failing to provide proper antecedent basis for the term "propylene glycine" recited in claim 22. Claim 22 has also been objected to as lacking antecedent basis for this limitation. The recitation of the term "propylene glycine" in claim 22 was an inadvertent typographical error. The claim should have read simply "glycine." This typographical error has been corrected by the present amendment. Support of this amendment is found in the specification at, *inter alia*, page 8, last full paragraph.

Claim 22 has been further objected to for the recitation of "essentially consisting of," rather than the conventional "consisting essentially of." Claim 22 has now been corrected to recite the conventional language.

II. Rejection Under 35 U.S.C. § 103(a)

A. Basis for the rejection

Presently pending claims 1-10, 12, 14, 15 and 18-23 were rejected under 35 U.S.C. § 103(a) as being obvious over US Patent No. 5,763,394 (O'Connor et al.). The Patent Office characterizes O'Connor et al. as describing an hGH formulation comprising hGH at a concentration of 1-20 mg/ml, a buffer system providing a pH of 5.5-7, a non-ionic surfactant, and a neutral salt. Office Action, page 3. The Patent Office acknowledges that the O'Connor et al. formulation "has no requirement for glycine." *Id.* The Patent Office further points out that glycine is an optional component of the formulation, but acknowledges that O'Connor et al. teach that glycine "provides 'less advantage in the aqueous formulations thereof' and allude[s] to the fact that glycine is more advantageous in preparations that have at some point been lyophilized." *Id.* The Patent Office further characterizes O'Connor et al. as describing the role of glycine in commercial formulations, "in the context of O'Connor et al.'s formulation having an unexpected advantage of being more stable with glycine absent, contrary to the common practice in the art." Office Action, pages 3-4. The Patent Office also points out that O'Connor et al. state that the commercially marketed hGH product Humatrope® comprises 5 mg/ml glycine. Office Action, page 4. The Patent Office states that O'Connor et al. describe a hGH formulation that is preferably isotonic and sterile. Finally, the Patent Office states that O'Connor et al. describe the following formulation components in the concentrations noted:

- phosphate, citrate and acetate buffers at a concentration of about 2-50 mM;

- non-ionic surfactants, including poloxamer and polysorbate, in the range of about 0.1-5 % w/v, with 0.1-1% w/v being preferred;
- preservative, including benzyl alcohol and phenol, in the range of about 0.7-1% w/v.

Office Action, pages 4-5. Based on this, the Patent Office concludes that claims 1-10, 12, 14, 15 and 18-23 are *prima facie* obvious over O'Connor et al., because

> [t]he prior art discloses all of the aspects and limitations of the instant invention, either specifically, such as the use of the surfactant Poloxamer 188, or with ranges of values that encompass or overlap those claimed by Applicant, such as the quantities of the active ingredient hGH, or as alternative choices of materials to be used to achieve the same result, such as the choice of buffer system or preservative.

According to the Patent Office

> [t]he claimed ranges and values of the amount of glycine that are greater than those typically found in the art are obvious in that it has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial result.

Office Action, page 5.

B. Applicants' response

The applicants respectfully submit that the Patent Office has not made a case for the *prima facie* obviousness of the present claims over O'Connor et al. As the Patent Office acknowledges, O'Connor et al. teach liquid hGH formulations that contain a "neutral salt." In fact, although O'Connor et al. states in the Summary of the Invention that

> One aspect of the invention is a stable, pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, and *optionally*, a neutral salt, mannitol and a preservative [col. 2, lines 28-32 (emphasis added)

all of the formulations disclosed in O'Connor et al. contain *either* mannitol *or* a neutral salt, with preferred embodiment of the disclosed formulations *consist of* or *consisting essentially of* hGH, nonionic surfactant, buffer and *either* a neutral salt *or* mannitol (e.g., col. 5, lines 7-14, Example IV, claims 1, 9, 18, 20, 21 and 23, Table 3). The invention of the present claims does not include either a neutral salt or mannitol. The teaching in O'Connor et al. that a neutral salt and/or mannitol is a necessary component in their liquid hGH formulation therefore teaches *away* from the invention of the present claims, which does not require either of these components.

Furthermore, the formulations taught in O'Connor et al. are stated to provide unexpected benefits *in the absence* of glycine (O'Connor et al., in fact, state at column 3, line 27, that "[t]he instant invention *has no requirement for glycine*" (emphasis added). At most, as acknowledged by the Patent Office, O'Connor et al. teach that glycine provides *some benefit* in *lyophilized* preparations. The present claims are directed toward liquid formulations of hGH, not lyophilized formulations. It is the clear teaching in O'Connor et al. that while glycine provides some benefit in a lyophilized formulation, it is preferably *omitted* from liquid hGH formulations –

in other words, O'Connor et al. also clearly teaches *away* from the present invention of a liquid hGH formulation comprising glycine.

In addition, the Patent Office makes no attempt to establish that O'Connor et al. teaches a liquid hGH formulation comprising hGH, glycine, a buffer, and a preservative, *which has a tonicity of from about 100 to about 500 mosm/kg*, as required by the present claims. The teaching in O'Connor et al. that a liquid formulation *lacking* glycine, and *including* a neutral salt or mannitol is "preferably isotonic" (NB: not "should be isotonic," in the imperative, as characterized by the Patent Office) is not sufficient to render obvious a formulation with a permissible *range* of tonicity as recited in the present claims, much less the very specific range recited. This is an affirmative limitation to the claims, which cannot be overlooked in the patentability analysis.

Finally, though the Patent Office concludes that it would have been *prima facie* obvious to "select optimal parameters" in a formulation "to achieve a beneficial result," such that modification of the O'Connor et al. teaching to arrive at the specific formulation parameters recited in the present claims, this principle does not apply in the present case, when the cited reference *teaches away* from the claimed formulation. O'Connor et al. teach that glycine should be *omitted* from liquid hGH formulations. Thus there is no reason or motivation for the skilled artisan to "optimize" the formulations taught by O'Connor et al. to *include* glycine at all, much less in the amounts specified in dependent claims 4, 5 and 22, which the Patent Office acknowledges *exceed* the amounts typically found in the art. A teaching to preferably omit glycine from a liquid hGH formulation cannot in any sense be taken as a teaching, suggestion, or motivation to include glycine in amounts greater than are even common in the art.

As a final point, the Patent Office does not apply the O'Connor et al. reference to claim 23, which recites "a kit comprising an injection device and a separate container containing a multi-dosage liquid formulation of human growth hormone according to claim 1." There is therefore no basis in the record for the rejection of claim 23 over O'Connor et al., or any other reference.

In view of the foregoing, the applicants respectfully submit that a case for the *prima facie* obviousness of the presently pending claims has not been established, and that the pending rejection of the claims under 35 U.S.C. § 103(a) can therefore properly be withdraw. Applicants respectfully request withdrawal of this rejection.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

The Patent Office has rejected claim 22 for failing to meet the enablement requirement of 35 U.S.C. § 112, first paragraph. The Patent Office states that the recited compound "propylene glycine" "is not found in the Chemical Abstracts Registry, nor is it found in any of the reference materials common to the pharmaceutical or pharmacological arts." Office Action, page 6.

The recitation of "propylene glycine" in claim 22 was an inadvertent typographical error. The claim should have read simply "glycine." This typographical error has been corrected by the

present amendment. Support for this amendment is found in the specification at, *inter alia* page 8, last full paragraph. Withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, the applicants respectfully submit that the claims are free of the prior art, and in condition for allowance, and that the pending rejections can properly be withdrawn. Favorable action on the claims is earnestly solicited

Respectfully submitted,

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